

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE**

TAKEDA PHARMACEUTICALS U.S.A., INC.,

Plaintiff,

v.

WEST-WARD PHARMACEUTICAL  
CORPORATION, HIKMA AMERICAS INC.,  
and HIKMA PHARMACEUTICALS PLC,

Defendants.

Civil Action No. 14-cv-1268

**Public Version of D.I. 46**

**DECLARATION OF SUSAN NEUFANG-TODD IN SUPPORT OF  
DEFENDANTS' SUPPLEMENTAL OPPOSITION TO PLAINTIFF'S  
MOTION FOR ENTRY OF A PRELIMINARY INJUNCTION**

I, Susan Neufang-Todd, declare as follows:

1. I submit this declaration in support of Intervenor-Defendants West-Ward Pharmaceutical Corporation (“West-Ward”), Hikma Americas Inc. and Hikma Pharmaceuticals PLC (all Intervenor-Defendants collectively “Hikma”) and in Opposition to Plaintiff Takeda Pharmaceuticals U.S.A., Inc.’s (“Takeda’s”) Motion for a Temporary Restraining Order and Preliminary Injunction (“Motion”).

2. I am the Senior Manager of Regulatory Affairs for West-Ward Pharmaceutical Corp. In this role, I reviewed copies of the letters and documents referenced herein and authored or received many of them myself. I have over 20 years’ experience in pharmaceutical regulatory affairs and am therefore familiar with FDA practice and procedure. Unless otherwise stated herein, I have personal knowledge of the facts set forth in this declaration, and if called as a witness, I could and would competently testify that the following facts are true and correct.

**I. History of Colchicine**

3. Colchicine is a naturally-occurring alkaloid derived from the *Colchicum autumnale* plant (commonly known as autumn crocus or meadow saffron), which has been recognized for its use in the treatment of gout since at least 6 AD. *See* Ex. 1 (Letter from Janet Woodcock, M.D., FDA Center for Drug Evaluation and Research (“CDER”), to Gary Veron regarding FDA Docket No. FDA-2010-P-0614, May 25, 2011), at 3. “On the basis of evidence that had built up over the years, numerous consensus guidelines recommended colchicine as an effective second-line treatment for gout...” Ex. 2 (Kesselheim et al., N.Engl.J.Med. 362:22 (June 3, 2010), 2045-47, *Incentives for Drug Development—The Curious Case of Colchicine*), at 2045.

4. Since the early 1970s, colchicine has also been used to treat familial Mediterranean fever (“FMF”). Colchicine “has long been considered the standard of care for

patients with this disorder.” Ex. 3, (Letter from Janet Woodcock, M.D., FDA’s CDER, to Gary Veron regarding FDA Docket No. FDA-2012-P-1018, Feb. 15, 2013), at 2.

5. Colchicine has been widely and inexpensively available as a generic drug in the United States since the 1800s. *See* Ex. 1 at 3; Ex. 2 at 2045. The 1938 Food, Drug, and Cosmetic Act (“FD&C”) required that new drugs be approved for safety prior to their introduction to the market, but old drugs could continue to be available. Colchicine is not merely old; it is literally ancient. *Id.*

6. West-Ward has manufactured colchicine tablets since at least 1972 and has sold more than *one billion* single-ingredient colchicine tablets. Until 2010, West-Ward was a leading supplier of colchicine in the United States.

7. Prior to 2009, colchicine as a lone active ingredient was not approved by the FDA, but combination drugs including colchicine as an active ingredient *were* approved for the prophylaxis of gout. In 1961, the FDA approved New Drug Application (“NDA”) No. 12-383 for ColBenemid, a fixed-dose oral combination of probenecid, 500 mg, and colchicine, 0.5 mg (approved to Merck). This approval was made prior to the 1962 amendments to the FD&C, which require proof of *efficacy* in addition to safety. In 1972 FDA completed a Drug Efficacy Study Implementation (“DESI”) review of ColBenemid and concluded that it was “effective for the treatment of chronic gouty arthritis when complicated by frequent, recurrent acute attacks of gout.” Ex. 1 at 4; 37 F.R. 15189 (July 28, 1972).

8. In 1976, Danbury Pharmacal, Inc. received approval of its Abbreviated New Drug Application (“ANDA”) No. 84-279, for Col-Probenecid, which referenced FDA’s approval of ColBenemid and the DESI supporting efficacy. Watson Labs is currently the owner of this ANDA. *See* Ex. 4 (Printout from Drugs@FDA).

9. Between July 29 and August 1, 2009, the FDA approved three NDAs for Colcrys<sup>®</sup>, which contain only colchicine as an active ingredient. These NDAs, Nos. 022-351,

-352, and -353 were filed by Mutual Pharmaceuticals Company, Inc. (“Mutual”) to obtain three different indications (approved uses) for Colcrys<sup>®</sup> tablets.<sup>1</sup> Each NDA was filed under Section 505(b)(2), and each NDA relied upon ANDA No. 84-279 for the combination drug Col-Probenecid. *See* Declaration of Arthur Tsien dated October 17, 2014 (“Tsien Decl.”),<sup>2</sup> at ¶ 29.

10. Because there were no Orange Book-listed patents for ANDA No. 84-279, Mutual would not have had to make a patent statement under Sec. 505(b)(2)(A). *See* Tsien Decl. ¶¶ 28, 31.

11. Mutual submitted no new nonclinical studies for its indication of treating “prophylaxis of gout flares” (which was the same indication received by ColBenemid in 1961). “The effectiveness of colchicine for this indication derived entirely from published literature and the DESI finding for ColBenemid (colchicine 0.5 mg/probenecid 500 mg), the listed drug relied upon.” Ex. 1 at 8. However, Colcrys<sup>®</sup> was granted three years of market exclusivity for its new indication for “treatment of acute gout flares,” even though this NDA (No. 22-351) closely followed guidelines promulgated by one of the major rheumatology professional societies years earlier in 2006. *See* Ex. 2 at 2046 (characterizing exclusivity as “surprising”). Shortly thereafter, Mutual began suing generic manufacturers of colchicine. *See id.*

12. On September 30, 2010, the FDA announced that it would halt marketing of colchicine by manufacturers without approved drug applications, including West-Ward. As requested, West-Ward stopped shipping generic colchicine within 90 days. This decision

---

<sup>1</sup> Mutual was a subsidiary of URL Pharma, Inc., which was purchased by Takeda in 2012 on the basis of large annual Colcrys<sup>®</sup> sales. All of URL Pharma’s other product lines were sold off by Takeda within six months of the acquisition. [http://articles.philly.com/2013-03-04/business/37412876\\_1\\_colcrys-url-pharma-takeda-pharmaceuticals](http://articles.philly.com/2013-03-04/business/37412876_1_colcrys-url-pharma-takeda-pharmaceuticals)

<sup>2</sup> I have reviewed Mr. Tsien’s declaration.

effectively raised prices on consumers and taxpayers from about nine cents per pill to nearly \$5. *Id.*

**II. FDA Expressly Permitted West-Ward to File a New Drug Application Under Section 505(b)(2) Based on the Same References Listed by Mutual**

13. West-Ward filed its New Drug Application (“NDA”) for Mitigare™ under subsection 505(b)(2) of the FD&C Act,<sup>3</sup> a regulatory pathway known in the pharmaceutical industry as a “505(b)(2)” or “Paper” NDA. These 505(b)(2) NDAs fit within the Hatch-Waxman statutory scheme, which is described in greater detail in the Declaration of Arthur Tsien dated October 17, 2014.

14. FDA’s approval of the Mitigare™ 505(b)(2) NDA was neither inexplicable nor forbidden by the FDA’s response to the Citizen Petition Mutual submitted November 26, 2010 (“2010 Citizen Petition”). *See* Ex. 1 (FDA’s response). In fact, FDA filings expressly permitted West-Ward’s 505(b)(2) NDA for Mitigare™. “The proposed regulatory pathway and the submitted clinical pharmacology data to support this application are reasonable.” Ex. 5 (Summary Review of NDA 204-820), at 1.

**A. West-Ward’s Colchicine Tablet 505(b)(2) NDA in 2010**

15. [REDACTED]

[REDACTED]

[REDACTED] West-Ward subsequently submitted IND Application No. 78601 for human studies on September 17, 2009. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

---

<sup>3</sup> This subsection is published at 21 U.S.C. § 355(b), but the FDA refers to the relevant sections as they are numbered in the FD&C Act, so I will follow this convention.

16. [REDACTED] West-Ward submitted New Drug Application [REDACTED] on September 1, 2010 (“2010 NDA”). [REDACTED]  
[REDACTED]  
[REDACTED]

**B. Mutual’s 2010 Citizen Petition**

17. Takeda’s subsidiary Mutual has known about West-Ward’s intent to file a 505(b)(2) NDA for single-ingredient colchicine since at least November 26, 2010, when Mutual submitted a citizen petition regarding West-Ward’s 2010 NDA. *See* Ex. 6 (Mutual Citizen Petition, Dkt. No. FDA-2010-P-0614) (“2010 Citizen Petition”). This petition explicitly stated “Mutual now believes that West-Ward...has submitted an application for a single ingredient oral colchicine...” *Id.*

18. In its citizen petition, Mutual argued that FDA should refrain from accepting or approving any application for a single-ingredient colchicine product *unless* that application was (1) filed as an ANDA and (2) references Mutual’s own 505(b)(2) NDA for Colcris<sup>®</sup>. *See id.* at 20.

19. Significantly, the FDA specifically *rejected* this request in its response to the 2010 Citizen Petition. *See* Ex. 1 (Letter to Veron re: Citizen Petition FDA-2010-P-0614, May 25, 2011). Not only did the FDA reject Mutual’s argument that any single-ingredient colchicine product must be filed as an ANDA, it further rejected Mutual’s argument that any single-ingredient colchicine application must list Colcris<sup>®</sup>:

We disagree with Mutual’s contention that any single-ingredient colchicine product submitted through the 505(b)(2) pathway must necessarily cite Colcris as its listed drug, irrespective of whether the proposed product shares the same strength, PK [pharmacokinetic] profile, or other characteristics such as dosage form or conditions of use. However, any 505(b)(2) application for a proposed single-ingredient colchicine product that is not a “duplicate” of Colcris must meet the statutory approval standard for safety and effectiveness.

See Ex. 1 at 20.

20. A dosage form is a different form of taking a drug by the same route of administration. For example, oral medications can be taken as a compressed (solid) tablet, a capsule (coating containing powdered compounds), or a liquid. Different dosage forms have different pharmacokinetic properties.

21. The FDA put the public on notice that it was appropriate for West-Ward, or any other party, to file an application seeking approval of one-ingredient colchicine product under Sec. 505(b)(2). The FDA simply clarified that any 505(b)(2) application could not be “duplicate” with the Colcrys<sup>®</sup> product.<sup>4</sup> The FDA explained that:

The informal term *duplicate* generally refers to a drug product that has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as a listed drug. See Abbreviated New Drug Application Regulations; Proposed Rule (54 FR 28872 at 28877, July 10, 1989). Certain products that are “duplicates” of a listed drug in these respects may, nevertheless, be appropriate for review and approval through the 505(b)(2) pathway because, for example, the pharmacokinetic profile is intentionally different from the listed drug. Compare 21 CFR 314.54(b) (describing situations in which a 505(b)(2) application may not be submitted).

Ex. 1 at 12 n.38; see also 21 n.67 (“published literature that does not expressly describe studies conducted with Colcrys or ColBenemid...may be relied upon by any 505(b)(2) applicant without necessitating citation of Colcrys or ColBenemid as a listed drug.”).

22. With this guidance, [REDACTED]

[REDACTED]

[REDACTED]

---

<sup>4</sup> The FDA also found that West-Ward’s 2010 NDA was a “duplicate” of Colcrys<sup>®</sup>, and therefore refused to accept that application even though the FDA previously and specifically advised that West-Ward’s filing under 505(b)(2) was acceptable. See *id.* at 17. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

C. [REDACTED]

23. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

24. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

See Confidential Ex.<sup>5</sup> Conf-3 [REDACTED]

[REDACTED].

25. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

26. [REDACTED]

[REDACTED]

---

<sup>5</sup> Confidential exhibits will be filed with the court under seal.

**D. West-Ward's Decision to Develop Mitigare™ and File New 505(b)(2) NDA as Suggested by the FDA**

27. I am familiar with the facts concerning West-Ward's decision to file a second 505(b)(2) NDA based on the new product Mitigare™, which uses a dosage form dissimilar to any previously-approved colchicine product: capsules.

28. First, [REDACTED]  
[REDACTED]. At no time [REDACTED]  
[REDACTED] was it suggested that a 505(b)(2) NDA would be rejected for failure to list Colcrys®. We had no obligation to reference Colcrys® and chose not to reference data for this product [REDACTED]. In fact, the FDA repeatedly suggested that [REDACTED] a 505(b)(2) NDA was appropriate. *See infra* and *supra* ¶¶ 14, 19, 21, 24, 36, 42, 47, and 53.

29. Second, we had further no desire to list Colcrys® as a reference because [REDACTED]  
[REDACTED]  
[REDACTED]. [REDACTED]  
[REDACTED] FDA had incorrectly advised that approval could be secured through an appropriately designed bioequivalence study with Col-Probenecid.<sup>6</sup> West-Ward spent significant sums on [REDACTED] the unaccepted 2010 NDA.

---

<sup>6</sup> This advice seemed especially reliable because Dr. Stanley Cohen, who was then acting President of the American Rheumatology Association called Mr. Raya and advised that he was calling on behalf of the FDA to inform Mr. Raya that the generic colchicine products could be approved based solely upon a bioequivalence comparison with Col-Probenecid.

These costs would be entirely for naught if West-Ward instead filed an ANDA referencing a different application such as the 505(b)(2) NDA for Colcrys®.

30. Third, [REDACTED]

[REDACTED] this course was preferable to West-Ward because 505(b)(2) applications are superior in some ways to ANDAs. Most importantly, submitting a 505(b)(2) allows faster approval and gives Ward-West a distinct advantage in a market that is likely to become crowded with ANDA filers down the road. All NDAs are subject to the Prescription Drug User Fee Act (PDUFA), which mandates that the FDA minimize approval time for new applications. As a result, review times for NDAs are dramatically shorter than for ANDAs; typically about ten months instead of years for most ANDAs.

31. With a 505(b)(2) NDA for a new dosage form, West-Ward could return to the colchicine market more quickly. Reintroducing competition to this market would benefit not only West-Ward, but also the patients, consumers, insurers, and government programs that currently overpay for an ancient drug that has become a monopoly with “no evidence of any meaningful improvement to public health.” Ex. 2 at 2046.

**E. Changes to Mitigare™ Product Label Were [REDACTED]  
[REDACTED] Supported by New Human Experiments**

32. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**1. More General Directions For Drug Interactions**

33. Rather than recommend a specific dosing regimen for dosing interactions during a gout flare, West-Ward proposed using more general directions to take smaller and less toxic doses—especially to manage drug interactions. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Confidential Ex. Conf-3 at 4.

34. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

35. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

*Id.* at 14-15.

36. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## **2. Carving Out Acute Gout Flare Instructions**

37. West-Ward also omitted directions from its proposed label that pertained to indications neither sought nor approved for Mitigare™. In this industry, such revisions are referred to as “carve outs.” As set forth in Declaration of Arthur Tsien, such carve outs are commonplace and are allowed by the FDA when the carve out does not diminish the safety or efficacy of a proposed drug compared to the referenced drug.

38. [REDACTED]

[REDACTED]

[REDACTED]

additional language was added to the NDA indicating stating that “safety and effectiveness...for acute treatment of gout flares during prophylaxis has not been studied.”

Ex. 7 (under “limitations of use”).

**3. [REDACTED] Hikma Performed the Human Studies Requested by the FDA**

39. West-Ward completed two different sets of pharmacokinetic (“PK”) studies in order to characterize the properties of Hikma’s new capsule formulation of colchicine.<sup>7</sup> [REDACTED]

[REDACTED] (1) comparative bioavailability of the new colchicine capsule versus Col-Probenecid and (2) drug-drug interaction studies to support Hikma’s proposed label.

40. The new PK studies show the absorption and metabolism of active ingredients for a particular formulation of a drug under various conditions. For example, FDA generally requires PK data for a new drug taken with food and on an empty stomach.

41. Additionally, [REDACTED] drug-drug interaction (“DDI”) [REDACTED] Hikma commissioned four DDI studies. One study was commissioned for each of [REDACTED] four drug types [REDACTED]: one each with a strong, moderate, and weak CYP3A4 inhibitor, and a P-gp inhibitor.

42. [REDACTED]

[REDACTED]

[REDACTED]

---

<sup>7</sup> For the capsule formulation, West-Ward Pharmaceuticals Corp. collaborated with Hikma Pharmaceuticals LLC to develop and submit the 2012 NDA of colchicine. [REDACTED] [REDACTED] for simplicity I will uniformly refer to the defendants as “Hikma” from this point forward.

[REDACTED]

Confidential Ex. Conf-5 [REDACTED] [REDACTED].

43. [REDACTED] Hikma prepared the 505(b)(2) NDA for Mitigare™

[REDACTED]

### III. Hikma's 505(b)(2) NDA For Mitigare™ ("2012 NDA")

44. On October 5, 2012, Hikma filed its 505(b)(2) New Drug Application ("2012 NDA"), No. 204-820, for its new capsule product, Mitigare™. This application does not rely at all upon *any* data from Takeda's application for Colcrys®. Instead, the application relies upon the published literature in support of colchicine's safety and efficacy including 49 journal articles and publications pertinent to colchicine dosing. Hikma also attached new human test results and referenced ANDA No. 84-279 for the colchicine-containing drug Col-Probenecid, which was approved as safe and efficacious in 1976.

45. Because there were no Orange Book-listed patents for Col-Probenecid, Hikma was not required to make a patent statement under Sec. 505(b)(2)(A)—just as Mutual was not required to make a patent statement for its similar 505(b)(2) NDAs. *See* Tsien Decl. ¶ 32.

46. Hikma's 2012 NDA entirely carved out indications and directions for acute gout flares *and* FMF. Given that Mitigare™ is a capsule instead of a tablet, many of Colcrys® directions concerning these indications could not be followed because capsules cannot be cut in half as tablets can be.

47. The FDA filed (accepted) the application October 25, 2012, suggesting that it did not find filing under 505(b)(2) inappropriate. [REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

48. Not once in this process did the FDA suggest that Hikma should instead file an ANDA, nor that a reference to Colcrys<sup>®</sup> was necessary to secure approval.

**A. Mitigare<sup>™</sup> is Unlike Colcrys<sup>®</sup>**

49. Hikma demonstrated Mitigare<sup>™</sup>'s safety and efficacy in part through new scientific data it obtained. These results show substantial differences in pharmacokinetics ("PK") between Mitigare<sup>™</sup> and Colcrys<sup>®</sup>, which justify approving different labels based on the different properties of these approved drugs. Mitigare<sup>™</sup> has a different PK profile than Colcrys<sup>®</sup>. In particular, some of the drastic dose reductions recommended by Takeda for Colcrys<sup>®</sup> appeared unwarranted for Mitigare<sup>™</sup>.

50. For example, whereas Mutual's DDI data suggested that co-administration with cyclosporine, a potent P-gp inhibitor, results in a 317% increase in blood concentration (and thus requires a 75% reduction in dose), another P-gp inhibitor, propafenon, was found to have virtually no effect on colchicine absorption from Mitigare<sup>™</sup>. *See* Ex. 8 at 15(FDA CDER Clinical Pharmacology and Biopharmaceutics Reviews for NDA No. 204-820).

51. In fact, none of the four CYP3A4 or P-gp inhibitors tested by Hikma had a significant impact on colchicine PK. The FDA carefully reviewed the literature suggesting such an effect and discerned that drug interactions had previously been reported for compounds that are *dual* inhibitors of CYP3A4 and P-gp. *See id.* at 13-15.

52. In other words, Mitigare<sup>™</sup> does "not appear to have a significant interaction with drugs" (Ex. 9 at 1)—at least not for "pure" CYP3A4 and P-gp inhibitors. Testing performed by Hikma demonstrated for the first time that not all CYP3A4 and P-gp inhibitors have deleterious effects on normal colchicine metabolism. Therefore, the highly specific and drastic label instructions for Colcrys<sup>®</sup> are unnecessary for Mitigare<sup>™</sup>. For these scientific

reasons—published literature and the results of Hikma’s four drug-drug interaction studies—the FDA approved a different label for Mitigare™ than Colcrys®:

As such, and based on these published case reports, general cautionary language informing health care providers and patients about drug-drug interaction potential of colchicine will be included in label [sic] along with simpler recommendations for close monitoring and dose adjustment based on clinical judgment if co-administered with dual inhibitors of CYP3A4 and P-gp as well as with CYP3A4 inhibitors or P-gp inhibitors. ...The applicant’s drug-drug interaction study results and published reports suggest that it may not be appropriate to recommend precise dose modifications based on one CYP3A4 inhibitor to another, or one P-gp inhibitor to another.

Ex. 5 (Summary Review of Regulatory Action for NDA No. 204-820), at 5.

53. The FDA regulatory briefing panel agreed with this general assessment immediately prior to approval, in September 2014. In fact, Hikma’s new data calls into question the label for Colcrys®:

The panel agreed that the West-Ward DDI studies raise questions about the generalizability of detailed dose modification recommendations to drugs that have not been directly studied and asked the team whether safety concerns had arisen based on the detailed dose modification recommendations in the Colcrys labeling. ...

The regulatory briefing panel also considered the labeling in light of FDA’s earlier consideration of drug-drug interaction information for colchicine in the context of a citizen petition submitted by Mutual in 2010. In FDA’s 2011 response to the citizen petition, FDA agreed that product labeling for single-ingredient oral colchicine products would need to include adequate information on drug-drug interactions and relevant dose adjustments needed to prevent unnecessary toxicity. However, in light of the new information provided by the West-Ward DDI studies, and the questions about the generalizability of dose modification recommendations, the regulatory briefing panel opined that it was reasonable to forego detailed dose modification recommendations and include Warnings and Precautions about drug interactions with colchicine based on the case reports in the literature, which suggest that dual inhibitors of CYP3A4 and P-gp are particularly problematic when administered with colchicine, and co-administration should be avoided.

Ex. 9 (FDA CDER Regulatory Briefing dated September 19, 2014), at 3.

54. Therefore, the FDA found Mitigare™'s label to be scientifically justified in light of Hikma's new results, which cast doubt on the generalizability of instructions previously submitted by Mutual and approved for Colcryst®.

**B. The FDA Approved Mitigare™ in Light of its Response to Mutual's 2010 Citizen Petition**

55. As shown by the block quote above, the FDA did not "inexplicably," negligently, or mistakenly grant approval of Mitigare™ without considering its prior decision on Mutual's 2010 Citizen Petition. The FDA was fully aware of its prior and consistent remarks on the 2010 Citizen Petition. See Ex. 9 at 3 (FDA "considered the labeling...in the context of a citizen petition submitted by Mutual in 2010."). Indeed, the FDA repeatedly discussed its response to Mutual's 2010 Citizen Petition before and after Hikma's 2012 NDA was filed. *See, e.g.*, Confidential Ex. Conf-3 at 4-5; Ex. 5 at 3; Ex. 9 at 2-3, 6 (Sept. 19, 2014 FDA briefing).

56. Instead, the FDA found that Hikma met "the statutory approval standard for safety and effectiveness" for a 505(b)(2) NDA. *Cf.* Ex. 1 at 20. Thus, on September 26, 2014 FDA approved Mitigare™ based on the 505(b)(2) NDA and the references relied upon therein.

**C. Mitigare™ is Not a Generic Form of Colcryst® and May Not be Substituted for Colcryst®**

57. Contrary to Takeda's assertions otherwise, Mitigare™ is not a "generic" version of Colcryst®.

58. Unlike ANDA applications under 505(j), 505(b)(2) applications generally do not obtain an "AB" equivalence rating, which is required for pharmacies to substitute the drug as a generic. This follows from the fact that 505(b)(2) NDAs are pertinently different from any previously-approved drug. *See* Ex. 1 at 20-21. The differences necessitating filing under Section 505(b)(2) typically mean that the drug is *not* interchangeable with any

particular referenced compound. For example, Mitigare™ is clearly not a substitute for the combination drug it references, Col-Probenecid, because it utterly lacks the active ingredient probenecid.

59. AB-status is doubly implausible for Mitigare™ with regard to Colcrys® because Colcrys® was *not even referenced in Hikma's NDA*. Further, no bioequivalence testing between the two 505(b)(2)-approved drugs was conducted. To the extent that DDI testing compared the two products, testing showed that Mitigare™ is radically different from Colcrys® in terms of drug interactions and metabolism.

60. In any event, Hikma does not seek therapeutic equivalence with Colcrys® and likely could not obtain such a rating even if it wanted to because of the substantial differences between Colcrys® and Mitigare™ discussed above.

61. Without AB-rating, prescriptions written for Colcrys® or colchicine tablets cannot and will not be substituted by pharmacists with Mitigare™. Therefore, Mitigare™ is a new drug that is not and cannot become a generic version of Colcrys®.

#### **IV. Mutual's 2012 Citizen Petition**

62. As Hikma was fulfilling the scientific and statutory standards for approving a new drug, Mutual submitted another Citizen Petition on September 21, 2012. In this petition Mutual asked the FDA to not approve any label that omitted (“carved out”) pregnancy-related data for the purportedly patented indication of familial Mediterranean fever (“FMF”). Mutual further argued that without this data on the label, an approved drug would be less safe than Colcrys®.

63. The FDA comprehensively rejected this petition in its response dated February 15, 2013:

We have carefully reviewed your Petition and have concluded that the clinical risk information in Colcrys labeling regarding use of colchicine by pregnant women with FMF is not information protected by patent or

exclusivity, and therefore may not be omitted on this basis from the labeling of a proposed generic drug that relies upon Colcrys. We also have concluded that even if clinical risk information regarding use of colchicine by pregnant women with FMF were determined to be within the scope of Colcrys' orphan exclusivity for FMF and were omitted from product labeling, it would not render a colchicine product less safe or effective than Colcrys for the treatment of acute gout flares or prophylaxis of gout flares.

Ex. 3 (Letter from Janet Woodcock, M.D., FDA's CDER, to Gary Veron regarding FDA Docket No. FDA-2012-P-1018), at 1.

64. The 2012 Citizen Petition had little direct impact on Hikma. Unlike several ANDA applicants, neither Hikma's 505(b)(2) NDA for Mitigare™ nor ANDAs based on Mitigare™ rely upon the Colcrys® 505(b)(2) NDA.

65. That said, FDA's denial of Mutual's Citizen Petition demonstrates that the omission of FMF data does not make Mitigare™ (or ANDAs based on Mitigare™) less safe than Colcrys®.

#### **V. Hardship of Preliminary Injunction**

66. West-Ward almost exclusively sells generic medications, which have relatively modest up-front costs for approval compared to 505(b)(2) NDA products. [REDACTED]

[REDACTED]

[REDACTED]

67. [REDACTED]

[REDACTED]

68. West-Ward was [REDACTED] [REDACTED] [REDACTED] being stopped in its tracks by the temporary restraining order issued by the District of Delaware on October 9, 2014. This restraining order causes tremendous disruption to both defendants' business, forfeits potential sales, [REDACTED] and strains relationships with defendants' distributors and suppliers.

69. Furthermore, the delay in marketing Mitigare™ (and its authorized generic)

[REDACTED]

[REDACTED] Because Hikma developed a new dosage form for colchicine, it was required to commission costly drug interactions studies not required from ANDA filers. The specific drug interactions tested were never before attempted in the published literature, and the FDA found that they provided fresh insights into colchicine interactions.


70. Defendants opted to file a much more expensive 505(b)(2) NDA so that it could return to the colchicine market more quickly. [REDACTED]

[REDACTED] The harm to defendant's respective operations, employees, and shareholders is enormous. Hikma and West-Ward are generic drug companies that do not sell any products grossing anywhere near \$600 million annually.

71. The harm to patients, doctors, and public health insurance programs that are currently forced to buy an unjustly monopolized colchicine product may be even greater. Defendants' entrance offers the public tangible benefits of choice and competition.

I declare under the penalty of perjury under the laws of the United States of America that, to the best of my knowledge, the foregoing is true and correct.

Dated: October 17, 2014

  
\_\_\_\_\_  
Susan Neufang-Todd